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RESEARCH HIGHLIGHT

Study clarifies associations between hypogonadism and health in aging men

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Tajar and colleagues present the associations between moderate and severe hypogonadism, symptoms of androgen deficiency and the prevelence of end-organ evidence of androgen deficency in 2966 older men in the European Male Aging Study. They find lower muscle mass, reduced bone mineral density, anemia, insulin resistence, metabolic syndrome and cardiovascular disease, with greater risks of these signs of androgen deficiency at lower serum testosterone concentrations.

There continues to be much discussion in the andrology community regarding the clinical significance of age-related declines in testosterone, and whether treatment of late-onset hypogonadism is warranted. Some observational studies have suggested that low testosterone in older men is associated with an increased risk of mortality,[1,2] while other studies have not found that low testosterone was associated with increased mortality when adjusting for other comorbidities.[3,4] In addition, interventional trials of testosterone have been unable to fully delineate the risks and benefits of testosterone therapy due to insufficient power and short treatment durations, even when aggregated in the form of a meta-analysis.[5] Moreover, one recent, placebo-controlled interventional study of testosterone in frail elderly men was stopped early by the data–safety monitoring board due to an excess of cardiovascular complications in men randomly assigned to the testosterone treatment arm,[6] raising concern that testosterone administration in older men may have significant drawbacks. Unfortunately, the uncertainty regarding the relative risk and benefits of testosterone therapy in elderly men with low testosterone is unlikely to be resolved in the near future as no sufficiently powered, long-term, prospective, randomized controlled trials of testosterone therapy in older men are underway. In the absence of such data, well-done observational studies offer patients and clinicians the best hope of understanding the clinical significance of late-onset hypogonadism.

The European Male Ageing Study is a large cohort of 2966 men aged 40–79 years from eight European countries designed to examine the associations between low testosterone and signs and symptoms of testosterone deficiency. The first cross-sectional report from this cohort demonstrated that sexual symptoms, including the trio of low *libido*, erectile dysfunction and diminished morning erections, were the type of symptoms most strongly associated with hypogonadism.[7] From this work, the authors proposed a definition of 'moderate' late-onset hypogonadism as the three sexual symptoms plus a total testosterone below 11 nmol l^{-1} and 'severe' late-onset hypogonadism as a testosterone of less than 8.0 nmol l^{-1}. Using these definitions, the authors now present data examining the associations between the degree of testosterone deficiency and end-organ evidence of androgen deficiency in the men in their cohort.[8] The important question being asked here is whether levels of serum testosterone that are significantly associated with sexual symptoms in aging men are also severe enough to lead to lower muscle mass, reduced bone mineral density, anemia, worsening insulin resistance, metabolic syndrome and cardiovascular disease. Of the 2966 men in the cohort, 63 (2.1%) were classified as having late-onset hypogonadism, with 36 (1.2%) meeting criteria for moderate late-onset hypogonadism and 27 (0.9%) men meeting criteria for having severe late-onset hypogonadism. Men with either moderate or severe late-onset hypogonadism tended to be older and more obese and have lower muscle mass, bone mineral density and hemoglobin than eugonadal men. Furthermore, men with either moderate or severe late-onset hypogonadism had lower mid-upper arm circumference and physical function compared to eugonadal men. However, only men with severe late-onset hypogonadism had significant associations between reduced testosterone and larger waist circumference, insulin resistance and metabolic syndrome. Interestingly, men with symptoms had greater evidence of end-organ involvement than men with low testosterone who lacked symptoms of androgen deficiency.

There are some key findings to this unique study. Firstly, the authors have demonstrated that the incidence of symptomatic hypogonadism in community-dwelling older men is lower than previously reported. For example, one analysis of American men suggested that 5% of older men were hypogonadal;[9] however, some of this difference may be due to older average age and greater average obesity levels in American men as compared with European men. Also, the authors find that men with symptoms are more likely to have end-organ involvement in association with low testosterone. In other words, symptoms of testosterone deficiency are an important clue to the severity of body's androgen deficiency state. This may be why symptomatic (as opposed to asymptomatic) late-onset hypogonadism is more strongly associated with multiple types of end-organ disease in the skeleton, bone marrow, muscle and adipose tissue. Furthermore, the authors nicely demonstrate that testosterone deficiency is a graded proposition, with some associations, such as metabolic syndrome, being much more pronounced only in men with severe hypogonadism, which was identified in 84% of these men! One limitation of the study is the fact that serum testosterone was measured on only one occasion. This can lead to misclassification in up to 50%

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of cases however, it is more likely for those classified as moderate than severe late-onset hypogonadism.[10]

Follow-up of men in this cohort was recently presented at an international research conference and suggests that severe late-onset hypogonadism is associated with a markedly increased risk of death over 4 years of follow-up. The andrology research community will eagerly await peer-reviewed publication of these results. In addition, this cohort will allow us to better understand the natural history of late-onset hypogonadism. For example, what proportion of men with moderate hypogonadism progress to severe hypogonadism over time, and what are the risk factors for this progression?

Obviously, an observational study such as the European Male Ageing Study is helpful in identifying associations, but it cannot prove causality as associations between low testosterone and outcomes could be confounded by overall health status. Nevertheless, the findings presented from European Male Ageing Study are extremely helpful in identifying the population of men best studied in future interventional trials. For example, studies examining the impact of testosterone administration on the metabolic syndrome should include men in with both symptoms of testosterone deficiency and serum testosterone concentration below 8 nmol l^{-1} as this group was much more likely to have metabolic syndrome. In addition, this study underscores the importance of enrolling symptomatic men in such trials as the presence of symptoms is an important sign of the severity of the body's androgen deficiency state. Furthermore, these data provide estimate of outcome effect sizes, which will be very useful in appropriate powering a randomized, interventional trial. Ultimately, it will take a large, prospective, long-term randomized clinical trial of testosterone therapy to accurately determine the relative risk to benefit ratio of testosterone therapy in age-related hypogonadism. In the meantime, the European Male Ageing Study has made an invaluable contribution to our understanding of the end-organ characteristics of androgen deficiency in older men with low testosterone concentrations.

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